

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Novial 28 film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

- Each yellow tablet contains 0.050 mg desogestrel and 0.035 mg ethinylestradiol;
- Each red tablet contains 0.100 mg desogestrel and 0.030 mg ethinylestradiol;
- Each white tablet contains 0.150 mg desogestrel and 0.030 mg ethinylestradiol.
- The green tablets do not contain active substances (placebo tablets).

Excipient: Lactose < 65mg

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

The tablets are round, biconvex and 5 mm in diameter. They are coded on one side “VR4” (yellow tablets), “VR2” (red tablets), “TR5” (white tablets) or “KH2” (green tablets). On the reverse side all tablets are coded “Organon” and an asterix “*”.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Contraception.

4.2 Posology and method of administration

How to take Novial 28

Tablets must be taken in the order directed on the package every day at about the same time with some liquid as needed. One tablet is to be taken daily for 28 consecutive days, starting with the yellow tablets for 7 days, followed by the red for 7 days and the white for 7 days and finally the green (inactive or placebo tablets) for 7 days. Each subsequent pack is started immediately following the last placebo tablet. During the placebo days a withdrawal bleed usually occurs. This usually starts on day 2-3 after the last tablet and may not have finished before the next pack is started.

How to start taking Novial 28

No preceding hormonal contraceptive use [in the past month]

Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). Starting on days 2-5 is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

Changing from a combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring, or transdermal patch).

The woman should start with Novial 28 preferably on the day after the last active tablet (the last tablet containing the active substances) of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC. In case a vaginal ring or transdermal patch has been used, the woman should start using Novial 28 preferably on the day of the removal, but at the latest when the next application would have been due.

All contraceptive methods (transdermal patch, vaginal ring) may not be marketed in all EU countries.

Changing from a progestogen-only-method (minipill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)

The woman may switch any day from the minipill (from an implant or the IUS on the day of its removal, from an injectable when the next injection would be due), but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

Following first-trimester termination of pregnancy

The woman may start immediately. When doing so, she need not take additional contraceptive measures.

Following delivery or second-trimester termination of pregnancy

For breastfeeding women see (*See section 4.6, Pregnancy and lactation*)

Women should be advised to start at day 21 to 28 after delivery or second-trimester termination of pregnancy. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

Management of missed tablets

If the user is **less than 12 hours late** in taking any tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If she is **more than 12 hours late** in taking any active tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. Active tablet-taking must never be discontinued for longer than 7 days.
2. 7 days of uninterrupted active tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly the following advice can be given in daily practice:

○ **Week 1 (yellow tablets)**

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets are missed and the closer they are to the regular placebo tablet interval, the higher the risk of a pregnancy.

○ **Week 2 (red tablets)**

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

- **Week 3 (white tablets)**

The risk of reduced reliability is imminent because of the forthcoming placebo tablet interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, the woman should be advised to follow the first of these two options and to use extra precautions for the next 7 days as well.

1. The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. The next pack must be started as soon as the active tablets in the current pack are finished, i.e., no placebo tablets should be taken. The user is unlikely to have a withdrawal bleed until the placebo tablet interval of the second pack, but she may experience spotting or breakthrough bleeding on active tablet-taking days.
2. The woman may also be advised to discontinue 'active tablet'-taking from the current pack. She should then immediately continue with the placebo tablets. The total number of missed tablets and placebo tablets must never exceed seven. Subsequently she should continue with the next pack.

- **Week 4 (green tablets)**

Contraceptive protection is not reduced, the woman should take further tablets at the usual time.

If the woman missed tablets and subsequently has no withdrawal bleed in the first normal placebo tablet interval, the possibility of a pregnancy should be considered.

Advice in case of gastro-intestinal disturbances

In case of severe gastro-intestinal disturbance, absorption may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3-4 hours after tablet taking, the advice concerning missed tablets as given in *section 4.2 (Posology and method of administration)*, is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) needed from another pack.

How to shift periods or how to delay a period

Delaying a period is not an indication for the product. However, if in exceptional cases a period needs to be delayed, the woman should continue with the white tablets from another pack of Novial 28 without a placebo tablet interval. The extension can be carried on for a maximum of 7 days (the white tablets in the second pack) During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of Novial 28 is then resumed after the usual 7-day placebo tablet interval.

To shift her period to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming placebo interval by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough bleeding and spotting during the second pack (just as when delaying a period).

4.3 Contraindications

Combined oral contraceptives (COCs) should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during COC use, the product should be stopped immediately.

- Presence or history of venous thrombosis (deep venous thrombosis, pulmonary embolism).
- Presence or history of arterial thrombosis (myocardial infarction, cerebrovascular accident) or prodromal conditions (e.g. transient ischaemic attack, angina pectoris).
- Known predisposition for venous or arterial thrombosis, such as Activated Protein C (APC) resistance, antithrombin-III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia and antiphospholipid antibodies.
- Recent severe or history of recurrent migraine both with focal neurological symptoms (*see section 4.4, Special warnings and precautions for use*)

- Diabetes mellitus with vascular involvement.
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (*see section 4.4, Special warnings and precautions for use*).
- Pancreatitis or a history thereof if associated with severe hypertriglyceridaemia.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex steroid-influenced malignancies (e.g. of the genital organs or the breasts).
- Endometrial hyperplasia.
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Hypersensitivity to any of the active substances of Novial 28 or to any of the excipients.

4.4 Special warnings and precautions for use

Warnings:

If any of the conditions/risk factors mentioned below is present, the benefits of COC use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether COC use should be discontinued.

1. Circulatory Disorders

- The use of any combined oral contraceptive carries an increased risk of venous thromboembolism (VTE) compared with no use. The incidence of VTE is considered to be 5-10 per 100,000 woman years in non-OC users. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. The risk of VTE associated with pregnancy is estimated as 60 cases per 100,000 pregnancies. VTE is fatal in 1-2% of cases.
- In several epidemiological studies it has been found that women using combined oral contraceptives with ethinylestradiol, mostly with a dose of 30 µg, and a progestin such as desogestrel have an increased risk of VTE compared with those using combined oral contraceptives containing less than 50 µg of ethinylestradiol and the progestin levonorgestrel.
- For brands containing 30 µg ethinylestradiol combined with desogestrel or gestodene compared with those containing less than 50 µg ethinylestradiol and levonorgestrel, the overall relative risk of VTE has been estimated to range between 1.5 and 2.0. The incidence of VTE for levonorgestrel containing combined oral contraceptives with less than 50 µg of ethinylestradiol is approximately 20 cases per 100,000 women-years of use. For Novial 28 the incidence is approximately 30-40 per 100,000 women-years of use: i.e. additional 10-20 cases per 100,000 women-years of use. The impact of the relative risk on the number of additional cases would be greatest in women during the first year they ever use a combined oral contraceptive when the risk for VTE with all combined oral contraceptives is highest.
- The risk of venous thromboembolism increases with:
 - Increasing age;
 - A positive family history (i.e. venous thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use;
 - Obesity (body mass index over 30 kg/m²);
 - Prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.
 - And possibly also with superficial thrombophlebitis and varicose veins. There is no consensus about the possible role of these conditions in the etiology of venous thromboembolism.

- The use of COCs in general has been associated with an increased risk of acute myocardial infarction (AMI) or stroke, a risk that is strongly influenced by the presence of other risk factors (e.g. smoking, high blood pressure, and age) (see also below). These events occur rarely. It has not been studied how Novial 28 modifies the risk of AMI.
- The risk of arterial thromboembolic complications increases with:
 - Increasing age;
 - Smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
 - Dyslipoproteinaemia;
 - Obesity (body mass index over 30 kg/m²);
 - Hypertension;
 - Migraine
 - Valvular heart disease;
 - Atrial fibrillation;
 - A positive family history (i.e. arterial thrombosis ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use.
- Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries, in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.
- Symptoms of venous or arterial thrombosis can include: unilateral leg pain and/ or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; ‘acute’ abdomen. Occurrence of one or more of these symptoms may be a reason for immediate discontinuation of Novial 28 usage.
- Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn’s disease or ulcerative colitis) and sickle cell disease.
- The increased risk of thromboembolism in the puerperium must be considered (*See section 4.6, Pregnancy and lactation*)
- An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.
- Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinaemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).
- When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with COC use.

2. Tumours

- Some epidemiological studies indicate that the long-term use of oral contraceptives displays a risk factor for the development of cervical cancer in women infected with human papillomavirus (HPV). However there is still controversy about the extent to which this finding is influenced by confounding effects, (e.g. differences in number of sexual partners or in use of barrier contraceptives).
- A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.
- In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

3. Other conditions

- Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.
- Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. A relationship between COC use and clinical hypertension has not been established. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the physician to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.
- The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.
- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.
- Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using COCs. However, diabetic women should be carefully observed while taking COCs.
- Crohn's disease and ulcerative colitis have been associated with COC use.
- Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.
- Novial 28 contains < 65mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on lactose-free diet should take this amount into consideration.

When counselling the choice of contraceptive method(s), all the above information should be taken into account.

Medical Examination/Consultation

Prior to the initiation or reinstatement of Novial 28 a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and if clinically indicated a physical examination should be performed, guided by the contra-indications (*See section 4.3, Contraindications*) and warnings (*see section 4.4, Special warnings and precautions for use*). The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of further periodic checks should be based on established practice guidelines and be adapted to the individual woman.

Women should be advised that oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmissible diseases.

Reduced efficacy

The efficacy of COCs may be reduced in the event e.g., missed tablets (*see section 4.2, Posology and method of administration*), gastro-intestinal disturbances (*see section 4.2, Posology and method of administration*) or concomitant medication (*See section 4.5, Interaction with other medicinal products and other forms of interactions*).

Herbal preparations containing St. John's wort (*Hypericum perforatum*) should not be used while taking Novial 28 due to the risk of decreased plasma concentrations and reduced clinical effects of Novial 28 (*See section 4.5, Interaction with other medicinal products and other forms of interactions*).

Reduced cycle control

With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women withdrawal bleeding may not occur during the tablet-free interval. If the COC has been taken according to the directions described in (*see section 4.2, Posology and method of administration*), it is unlikely that the woman is pregnant. However, if the COC has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

4.5 Interaction with other medicinal products and other forms of interaction**Interactions**

Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or oral contraceptive failure. The following interactions have been reported in the literature.

Hepatic metabolism: interactions can occur with drugs that induce microsomal enzymes, which can result in increased clearance of sex hormones (e.g., hydantoins, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, ritonavir, griseofulvin and products containing St. John's wort). Maximal enzyme induction is generally not seen for 2-3 weeks but may then be sustained for at least 4 weeks after the cessation of drug therapy.

Contraceptive failures have also been reported with antibiotics, such as ampicillin and tetracyclines. The mechanism of this effect has not been elucidated.

Women on treatment with any of these drugs should temporarily use a barrier method in addition to the COC, or choose another method of contraception. With microsomal enzyme-inducing drugs, the barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. In case of long term treatment with microsomal enzyme-inducing drugs another method of contraception should be considered. Women on treatment with antibiotics (except rifampicin and griseofulvin) should use the barrier method until 7 days after discontinuation. If the period during which the barrier method is used runs beyond the end of the tablets in the COC pack, the next COC pack should be started without the usual tablet-free interval.

Oral contraceptives may affect the metabolism of other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g., cyclosporine) or decrease (e.g. lamotrigine).

Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

Laboratory tests

The use of contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis.

Changes generally remain within the normal laboratory range.

4.6 Pregnancy and lactation

Novial 28 is not indicated during pregnancy. If pregnancy occurs during treatment with Novial 28, further intake should be stopped. However, most epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy.

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of COCs should generally not be recommended until the nursing mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk, but there is no evidence that this adversely affects infant health.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

Possibly related undesirable effects that have been reported in users of Novial 28 or COC users in general are listed in the table below¹:

| System Organ Class | Common/ ($> 1/100$) | Uncommon ($> 1/1000$ and <100) | Rare ($< 1/1000$) |
|--|--------------------------------|---------------------------------------|---------------------------------------|
| Immune system disorders | | | Hypersensitivity |
| Metabolism and nutrition disorders | | Fluid retention | |
| Psychiatric disorders | Depressed mood, mood altered | Libido decreased | Libido increased |
| Nervous system disorders | Headache | Migraine | |
| Eye disorders | | | Contact lens intolerance |
| Gastrointestinal disorders | Nausea, abdominal pain | Vomiting, diarrhea | |
| Skin and subcutaneous tissue disorders | | Rash, urticaria | Erythema nodosum, erythema multiforme |
| Reproductive system and breast disorders | Breast pain, breast tenderness | Breast hypertrophy | Vaginal discharge, breast discharge |
| Investigations | Weight increased | | Weight decreased |

¹ The most appropriate MedDRA term (version 8.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

A number of undesirable effects have been reported in women using combined oral contraceptives (*see section 4.4, Special warnings and precautions for use*). These include: venous thromboembolic disorders; arterial thromboembolic disorders; hypertension; hormone-dependent tumours (e.g. liver tumours, breast cancer); chloasma.

4.9 Overdose

There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in this case are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Classification: G03AB05

The contraceptive effect of COCs is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the cervical secretion. As well as protection against pregnancy, COCs have several positive properties which, next to the negative properties (*See section 4.4, Special warnings and precautions for use and 4.8, Undesirable effects*), can be useful in deciding on the method of birth control. The cycle is more regular and the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency. Apart from this, with the higher dosed COCs (50 µg ethinylestradiol) there is evidence of a reduced risk of fibrocystic tumours of the breasts, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy and endometrial and ovarian cancer. Whether this also applies to lower-dosed COCs remains to be confirmed.

In clinical studies it has been shown that Novial 28 significantly reduced the androgenic parameters 3- α androstenediol-glucuronide, androstenedione, DHEA-S and free testosterone.

5.2 Pharmacokinetic properties

Desogestrel:

ABSORPTION

Orally administered desogestrel is rapidly and completely absorbed and converted to etonogestrel. Peak serum concentrations of approximately 1.5 ng/ml (first week) to 5 ng/ml (third week) are reached at about 1.5 hours. Bioavailability is 62 - 81 %.

DISTRIBUTION

Etonogestrel is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 2 - 4 % of the total serum drug concentrations are present as free steroid, 40 - 70 % are specifically bound to SHBG. The ethinylestradiol-induced increase in SHBG influences the distribution over the serum proteins, causing an increase of the SHBG-bound fraction and a decrease of the albumin-bound fraction. The apparent volume of distribution of desogestrel is 1.5 l/kg.

METABOLISM

Etonogestrel is completely metabolized by the known pathways of steroid metabolism. The metabolic clearance rate from serum is about 2 ml/min/kg. No interaction was found with the co-administered ethinylestradiol.

ELIMINATION

Etonogestrel serum levels decrease in two phases. The terminal disposition phase is characterized by a half-life of approximately 30 hours. Desogestrel and its metabolites are excreted at a urinary to biliary ratio of about 6:4.

STEADY-STATE CONDITIONS

Etonogestrel pharmacokinetics are influenced by SHBG levels, which are increased threefold by ethinylestradiol. Following daily ingestion, drug serum levels increase about two- to threefold, reaching steady state conditions during the second half of the treatment cycle.

Ethinylestradiol:

ABSORPTION

Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 80 pg/ml are reached within 1-2 hours. Absolute bioavailability as a result of presystemic conjugation and first-pass metabolism is approximately 60%.

DISTRIBUTION

Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98.5%) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 5 l/kg was determined.

METABOLISM

Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulfate. The metabolic clearance rate is about 5 ml/min/kg.

ELIMINATION

Ethinylestradiol serum levels decrease in two disposition phases, the terminal disposition phase is characterized by a half-life of approximately 24 hours. Unchanged drug is not excreted; ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

STEADY-STATE CONDITIONS

Steady state concentrations are reached after 3-4 days when serum drug levels are higher by 30 - 40% as compared to single dose.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans when COCs are used as recommended. This is based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. However, it must be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients***Tablet core*

All-rac- α -Tocopherol
lactose monohydrate
potato starch
povidone
silica colloidal anhydrous
stearic acid

Tablet core (Placebo Tablets)

Lactose monohydrate
magnesium stearate
maize starch

FILM-COATING

Ferric oxide red (E 172)*

ferric oxide yellow (E 172)**

Indigo carmine lake (E 132)***

hypromellose

macrogol 400

talc

titanium dioxide (E 171)

* only in 0.100 mg desogestrel/0.030 mg ethinylestradiol tablets (red tablets)

** only in 0.050 mg desogestrel/0.035 mg ethinylestradiol tablets (yellow tablets) and placebo tablets (green tablets)

*** only in placebo tablets (green tablets)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package.

6.5 Nature and contents of container

PVC/aluminium blister which is packed in an aluminium laminated sachet.

Pack sizes: 28, 3 X 28 and 6 X 28 tablets.

Each blister contains 28 tablets (7 yellow, 7 red, 7 white tablets and 7 green tablets).

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Organon (Ireland) Limited

P O box 2857

Drynam Road

Swords

Co. Dublin

Ireland

8 MARKETING AUTHORISATION NUMBER

PA 0061/006/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 May 2000

Date of last renewal: 04 November 2006

10 DATE OF REVISION OF THE TEXT

June 2007